Primary Aldosteronism

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Diagnostic Considerations

Primary aldosteronism (PA) is the most common cause of endocrine hypertension. Patients with PA have higher cardiovascular morbidity and mortality compared with age- and sex-matched patients with essential hypertension and the same degree of blood pressure elevation.

Case detection screening should be considered in patients with:

- Spontaneous hypokalemia, including patients treated with low-dose thiazide diuretics. However, there are patients with primary mineralocorticoid excess who are normokalemic and rarely some who are hypokalemic but normotensive. Only 9–37% of patients with primary aldosteronism are hypokalemic.
- Severe or resistant hypertension to three conventional antihypertensive drugs (including a diuretic) or controlled BP (<140/90 mm Hg) requiring four or more antihypertensive drugs.
- Patients with hypertension and adrenal incidentaloma.
- Hypertension and a family history of early-onset hypertension or cerebrovascular accident at a young age (<40 years).
- Hypertensive first-degree relatives of patients with PA.

Inpatient Testing for Hyperaldosteronism

The recommended case detection-screening test is the plasma aldosterone activity (PAC)/plasma renin activity (PRA).

An elevated plasma aldosterone activity (PAC)/plasma renin activity (PRA) ratio and an increased PAC are required for the diagnosis of primary aldosteronism.

- PAC is inappropriately high for the PRA, usually >15 ng/dL.
- PAC/PRA ratio greater than 20.

Collecting blood midmorning from seated patients following 2–4-h upright posture improves sensitivity.

In the setting of spontaneous hypokalemia, plasma renin below detection levels plus plasma aldosterone concentration (PAC) >20 ng/dL, further confirmatory testing might not be needed.

Confirmatory Testing Usually, elevated PAC/PRA ratio alone does not establish the diagnosis of primary aldosteronism, and the results have to be confirmed by demonstrating inappropriate aldosterone secretion, except in situations as spontaneous hypokalemia, undetectable PRA or PRC, and a PAC >20 ng/dL. Otherwise, aldosterone suppression testing is needed with one of several tests (table of confirmatory test).

The patient that presents with hypertensive crisis despite the use of multiple antihypertensives should be screened for primary hyperaldosteronism.

Factors Affecting Aldosterone/Renin Ratio

False Negatives Genrally limited to the mineralocorticoid receptor antagonists, spironolactone and eplerenone. While dietary salt restriction, concomitant malignant or renovascular hypertension, pregnancy, and treatment with diuretics (including spironolactone), dihydropyridine calcium blockers, angiotensin-converting enzyme inhibitors, and angiotensin receptor antagonists can stimulate renin, they generally do not have a sufficiently potent effect to interfere with diagnosing PA.

False Positives Beta-blockers, alpha-methyldopa, clonidine, and nonsteroidal anti-inflammatory drugs suppress renin, raising the ARR with potential for false positives. False positives can also occur in patient with advanced age and renal disease.

In general, medications other than the minetarlocorticoid antagonists do not need to be discontinued before ARR measurement. However, when the diagnosis is not clear, the interfering medications should be discontinued at least 2 weeks before ARR measurement; diuretics should be discontinued ideally 6 weeks before the test, although this is inconvenient, potentially harmful and rarely feasible. Some patients will require substitution of the

interfering medication during the washout period until the test is completed. Doxazosin and fosinopril can be used in hypertensive patients who need to undergo aldosterone and PRA measurement for the diagnosis of primary aldosteronism; amlodipine yields a small percentage of false-negative diagnoses, and beta-blockers may only have limited influence on the diagnosis of primary aldosteronism as they lower PRA and PRC measurements and raise the PAC/PRA ratio, an effect that in most settings is not clinically significant. Other potassium-sparing diuretics, such as amiloride and triamterene, usually do not interfere with testing unless the patient is treated with high doses.

Special Considerations: Cortisol Co-secretion

There is an increasing awareness of cortisol co-secretion in the context of primary hyperaldosteronism resulting from adrenal tumors. Overt or subtle glucocorticoid hypersecretion may potentially interfere with diagnostic studies or result in secondary/tertiary adrenal insufficiency after surgical removal of the tumor because of contralateral gland suppression. Patients with adrenal tumors, including those with confirmed hyperaldosteronism, should also be evaluated for hypercortisolism with a 1 mg dexamethasone suppression test.

Disease Subtyping

Once the diagnosis of primary hyperaldosteronism has been confirmed, unilateral adenoma or rarely carcinoma must be distinguished from bilateral disease. Disease subtyping is established using adrenal computed tomography (CT) and adrenal vein sampling (AVS) (algorithm). Adrenal vein sampling is used to distinguish between unilateral adenoma and bilateral hyperplasia, and it is recommended to confirm unilat-

eral secretion for patients who would likely pursue surgical management.

Treatment

The curative treatment is surgical: unilateral laparoscopic adrenalectomy for patients with documented unilateral PA or unilateral adrenal hyperplasia.

Medical treatment is preferred in patients who are unable or unwilling to undergo surgery or who have bilateral adrenal disease. Mineralocorticoid receptor antagonists are the medical treatment of choice. Spironolactone is the primary agent at doses ranging from 25 to 400 mg/d, with eplerenone as an alternative. Antiandrogen side effects such as gynecomastia and diminished libido in men and menstrual disorders in women can result from spironolactone due to cross-antagonism of the sex steroid receptor. Eplerenone is more specific for the aldosterone receptor and therefore causes less undesired side effects but is less potent than spironolactone. In a study comparing these two therapies, spironolactone at doses ranging from 75 to 225 mg/d was more efficacious than eplerenone at doses between 100 and 300 mg/d for hypertension control. Biochemical cure following adrenalectomy as well as hemodynamic improvement is seen in over 90% of patients. Hypokalemia typically resolves immediately after surgery, and blood pressure reduction may take months, prompting a reduction in quantity of antihypertensive medications in most patients.

Early Postoperative Period

We suggest the measurement of aldosterone and PRA on the first and second postoperative day. A significant decrease in serum aldosterone levels is detected a few hours after adrenal clipping is performed during adrenalectomy, although plasma renin activity may take weeks to normalize.

In general, when the unilateral adrenalectomy is successful, aldosterone levels achieve a nadir within 24–48 h after the intervention, suggesting cure. After surgery, mineralocorticoid receptor antagonists should be withdrawn in the first postoperative day to avoid hyperkalemia. Antihypertensives should be administered base on the patient's postoperative blood pressure readings. One should expect a significant reduction in the number of antihypertensives and dosing in most cases. On occasion, normotension is observed in the early postoperative period, particularly in younger patients with less severe preoperative hypertension, although blood pressure normalization may take up to a year to occur. Unless the patient is persistently hypokalemic, postoperative hydration should include normal saline without potassium with careful monitoring of renal function, as a decrease in GFR is often seen following resolution of hyperaldosteronism, a condition that results in glomerular hyperfiltration. Preoperative renal damage as revealed by elevated serum creatinine and microalbuminuria are significant predictors of postoperative hyperkalemia (hypoaldosteronism).

Hence, the combination of worsening renal function and postsurgical hypoaldosteronism that occurs in cured patients treated with unilateral adrenalectomy may result in severe hyperkalemia, requiring close attention not only in the early postoperative period but also following discharge. Because the hypoaldosteronism may be prolonged, we recommend at least weekly electrolyte and renal function testing during postsurgical month, as a minimum.

Special Considerations

Primary Hyperaldosteronisms and Pregnancy

Primary aldosteronism is uncommon in pregnancy, with only few cases reported in the literature, most of them due to aldosterone-producing adenomas. Primary aldosteronism can lead to

intrauterine growth retardation, preterm delivery, intrauterine fetal demise, and placental abruption.

The evaluation in the pregnant woman is the same as for non-pregnant patients. For case confirmation, however, the captopril stimulation test is contraindicated in pregnancy, but measurement of sodium and aldosterone in a 24-h urine collection is an option. Subtype testing with abdominal magnetic resonance imaging (MRI) without gadolinium is the test of choice. Computed tomography (CT) and adrenal venous sampling are contraindicated in pregnancy.

Hypertension may improve or worsen in pregnancy due to the agonist/antagonist function of progesterone on the mineralocorticoid receptor.

The treatment depends on the case presentation including medical or surgical options:

- Unilateral laparoscopic adrenalectomy during the second trimester in clear cases of tumors of >1 cm.
- Spironolactone crosses the placenta and is a US Food and Drug Administration (FDA) pregnancy category C (Not proven safe in pregnancy), and eplerenone is an FDA pregnancy category B (There are no adequate and well-controlled studies in pregnant women. Should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus). Therefore, standard antihypertensive drugs approved for use during pregnancy should be used.
- Hypokalemia can be managed with oral potassium supplements.

The Patient with Chronic Kidney Disease

The diagnosis of primary hyperaldosteronism could be challenging in patient with chronic kidney disease (CKD) as this may

disturb the renin-angiotensin-aldosterone system. The diagnosis of primary PA in the CKD population has not been established as plasma aldosterone concentration, PRA, and ARR can vary significantly in CKD. As CKD progresses, PAC increases, and the more advanced the CKD, the lesser the effect on PRA, giving rise to a higher ARR. Also in a study, primary aldosteronism patients accompanying chronic kidney disease had high serum aldosterone and ARR levels, low PRA, and no clear association of hypokalemia.

Familial Hyperaldosteronism: Contact with the Family Members

Familial hyperaldosteronism is a group of inherited conditions inhered in an autosomal dominant pattern. Three familial forms of PA have been described:

- FH type I or glucocorticoid-remediable aldosteronism, usually associated with bilateral adrenal hyperplasia.
- FH type II is not dexamethasone suppressible.
- FH type III is caused by germ line mutations in the potassium channel subunit KCNJ5, mostly suspected in patient with massive adrenal hyperplasia and children.

The patient and their family should receive appropriate information as well as appropriate counseling for biochemical screening of family members; continuously updated databases of human genes and genetic disorders and traits like OMIM or MalaCards are excellent free educational resources (Fig. 21.1).

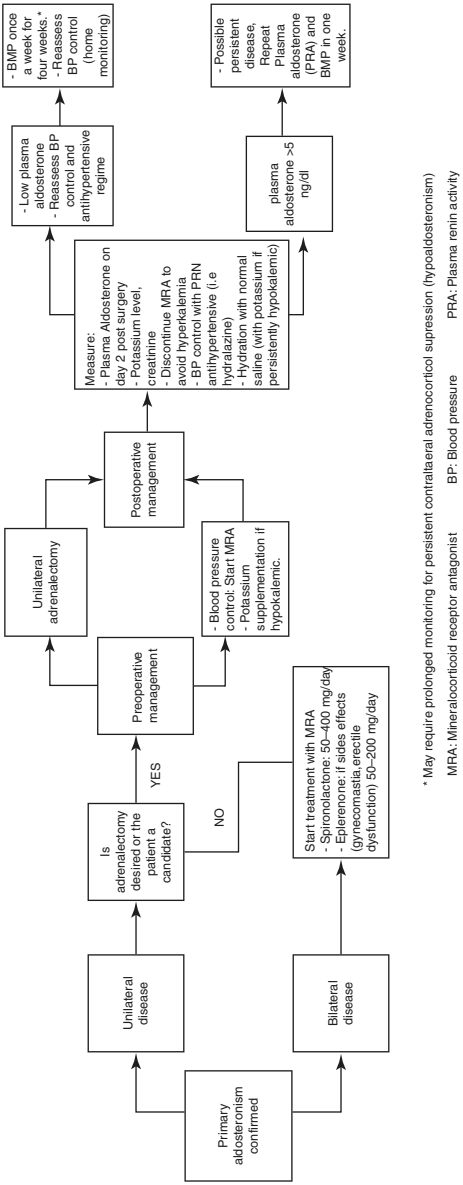

Fig. 21.1 *Algorithm:* inpatient management of primary hyperaldosteronism

Suggested Reading

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